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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,219	03/11/2004	Matilde Bustos De Abajo	U 015070-8	3487

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
06/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,219	ABAJO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-18 and 28-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14 and 28-30* is/are allowed.

6)☒ Claim(s) *12,13,15-18 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/09 has been entered. Applicant's amendment and response received on 3/26/09 have been entered. Claims 1-11 and 19-27 are canceled, and new claims 34-39 have been added. Claims 12-18 and 28-39 are pending and under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Objections

The objection to claim 32 under 37 CFR 1.75(c), is withdrawn in view of the amendment to claim 32 which now depends on claim 31.

Claim Rejections - 35 USC § 112

The rejection of pending claims 12-18 and 28-33 under 35 U.S.C. 112, first paragraph, for scope of enablement, is withdrawn in view of applicant's amendments to the claims and

arguments, the evidence of the WO 95/29237 publication for administration of CT-1, and the previously filed Declaration by Dr. Valtuena.

Please note that the following new art rejections have been found to apply.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-33 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Richards et al. (1996) Interferon and Cytokine Research, Vol. 16, 69-75. The applicant claims methods for stimulating the proliferation or, or for the protection against apoptosis of , liver cells *in vitro*, said method comprising the step of treating liver cells *in vitro* with cardiotrophin-1 (CT-1) in an amount effective for the proliferation or protection.

Richards et al. teaches the treatment of primary liver cells with CT-1 *in vitro* in an amount sufficient to trigger intracellular signaling and induce gene expression in the treated hepatocytes (Richards et al., page 69 and 71-72). Richards et al. further teaches that stimulation of hepatocytes with CT-1 occurred in a dose range from 0.05-5 nM (0.1-100 ng/ml), which is consistent with the effective concentrations of CT-1 in other assays previously reported in the literature (Richards et al., pages 69 and 73).

Although Richards et al. was interested in the effects of CT-1 on the acute phase response in hepatocytes and did not test the effects of CT-1 on proliferation or protection from apoptosis, Richards et al. teaches the exact same method step as recited in the instant claims- treatment of liver cells *in vitro* with an effective amount of cardiotrophin-1 (CT-1) to stimulate hepatocytes. It is further noted that the concentration range of CT-1 taught to be effective by Richards, 0.1-100 ng/ml, includes the concentration of 50 mg/ml taught by the specification to be effective *in vitro* in inducing hepatocyte proliferation or protecting the cells from serum starvation induced apoptosis. Thus, Richards et al. does in fact teach treating hepatocytes *in vitro* with cardiotrophin-1 (CT-1) in an amount effective for the proliferation or protection of hepatocytes.

The applicant is reminded that it is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). The MPEP also states that "when the claim recites using an old composition or structure and the 'use' is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F. 2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)". MPEP 2112.02. Therefore, by teaching the exact method step recited in the claims as written, Richards et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-13, 15-18, and 31-39 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Jin et al. (1996) Cytokine, Vol. 8 (12) 920-926 (of record), in view of US Patent Application Publication 2002/0187936 (2002), hereafter referred to as Costa et al., and US Patent 6,719,969 (2004), hereafter referred to as Hogaboam et al. The applicant claims methods of treating a subject whose liver has experienced a loss of functional liver cells comprising administering to the subject CT-1 in an amount effective for stimulating hepatocyte proliferation. The applicant further claims said methods where the subject has undergone or will undergo surgical hepatectomy or a liver transplant, suffers from hepatitis or cirrhosis, or where the loss of cells is the result of a toxin, an autoimmune disease, a viral infection such as hepatitis.

Jin et al. teaches methods for the *in* vivo administration of cardiotrophin-1 (CT-1) protein and specifically methods for administering CT-1 comprising the i.p. administration of 2ug of cardiotrophin twice a day for 14 days to a subject resulting in liver growth (Jin et al., page 921-

922, Table I and Figure 2, and page 925). Thus, Jin et al. by showing that CT-1 induces liver growth *in vivo* demonstrate that CT-1 can stimulate hepatocyte proliferation and/or differentiation.

Jin et al. differs from the instant methods by not teaching to administer CT-1 to a subject whose liver has experienced a loss of functional liver cells, whether through surgical hepatectomy, hepatitis, hepatic cirrhosis, ischemia, or exposure to a toxic agent. However, at the time of filing, Costa et al. and Hogaboam et al. teach that proteins which induce proliferation of hepatocytes can be effectively administered to subjects with liver damage in order to stimulate hepatocyte proliferation. Specifically, Costa et al. teaches the administration of growth hormones, or other proteins that induce the FoxM1B transcription factor and induce hepatocyte proliferation, can be used to prevent or ameliorate liver damage or disease in patients (Costa et al, abstract and pages 1,3, 10, and 15-16). Costa et al. provides further guidance for the various causes of liver damage and disease which can be treated using a protein that stimulates hepatocyte proliferation, including liver transplantation, autoimmune disease, toxins (environmental and specifically hepatotoxic), viral infections such as hepatitis, cirrhosis, and mechanical injury (Costa et al., pages 9-10). Costa et al. also teaches to administer the protein before and/or after partial hepatectomy (Costa et al., page 23). Further, Costa et al. provides extensive guidance for pharmaceutical formulations and for determining effective dosages (Costa et al., pages 10 and 14-16). Hogaboam et al. also teaches the administration of a variety of proteins, all of which induce hepatocyte proliferation, to patients with liver damage, where the liver damage is the result of viral infections such as hepatitis, exposure to toxins, such as acetaminophen overdose, alcohol, or liver resection (Hogaboam et al., columns 5-6). Hogaboam

et al. teaches that many proteins posses the capability to stimulate liver regeneration including CXC chemokines, HGF, SCF, TNF-alpha, and IL-6 (Hogaboam et al., columns 6, and 15). Like Costa et al., Hogaboam et al. also provides extensive guidance for pharmaceutical formulations of protein for *in vivo* administration and dosages (Hogaboam et al., columns 5-9, and 45-48). Thus, the combined teachings of Costa et al. and Hogaboam et al. provide motivation and a reasonable expectation of success to administer proteins with hepatocyte proliferative properties to subjects suffering from liver damage due to a wide variety of causes to induce hepatic regeneration.

Therefore, in view of the motivation provided by Costa et al. and Hogaboam et al. to administer protein with hepatoproliferative properties to subjects whose livers have a loss of functional liver cells, and the teachings of Jin et al. that CT-1 has hepatoproliferative activity *in vivo* as evidenced by an observed increase in liver size following CT-1 administration, it would have been *prima facie* obvious to the skilled artisan at the time of filing to practice the method of administering CT-1 protein taught by Jin et al. in patients with liver damage, or alternatively to substitute CT-1 for one of the proteins in the methods of inducing hepatocyte proliferation and ameliorating liver damage taught by Costa et al. and Hogaboam et al. One of skill in the art at the time of filing would have had a reasonable expectation of success in using CT-1 to stimulate hepatocyte proliferation in patients with liver damage based on the demonstration by Jin et al. that CT-1 increase liver size *in vivo*, and/or because the simple substitution of one protein with hepatoproliferative properties for another in the methods of Costa et al. or Hogaboam et al. would have yielded the predictable result of hepatocyte proliferation.

Allowable Subject Matter

Claims 14 and 28-30 appear to be free of the prior art of record and are considered allowable at this time.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633